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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,642	11/12/2003	Gloria C. Li	1747 / 55672-AA-PCT-US/JP	8975

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,642	LI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 11-12-02.

Claims 27-40 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising the administration of antisense oligonucleotides that specifically hybridize with any nucleic acid molecule encoding Ku70, inhibit its expression in vitro or in in vivo, and provide for treatment effects in a subject. The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising these compounds that specifically hybridize and inhibit the expression of Ku70 and provide treatment effects in a subject. The specification discloses the polynucleotide sequence encoding human Ku70 and various mutations in human Ku70 that are associated with primary tumors.

The specification does not disclose any antisense sequences, including any sequences with less than 100% identity to the complement of human or other sources of Ku70, that specifically hybridize and inhibit its expression in vitro or in vivo and that, upon administration to a subject, provide for treatment effects. The genus of nucleic acids claimed encompasses a myriad of structures (*e.g.* thousands of nucleic acid sequences) and the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure. No common structural attributes identify the members of the claimed genus, and distinguish members within the claimed genus from those outside of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, antisense oligonucleotides that specifically hybridize and inhibit the expression of any nucleic acid encoding Ku70, inhibit its expression in vitro or in vivo and provide for treatment effects as claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 27-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of increasing a target cell's susceptibility to DNA damaging agents comprising the administration of antisense that inhibit the expression of human Ku70, does not reasonably provide enablement for in vivo methods, and further whereby treatment has been provided in an organism. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to pharmaceutical compositions and methods of treating tumors in a subject comprising administration of an antisense, optionally expressed from an adenoviral vector under control of a heat shock promoter, that specifically hybridizes to and inhibits the expression of Ku70.

The state of the prior art and the predictability or unpredictability of the art. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of nucleic acid molecules to appropriate cells in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Res. & Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross

biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: Alt is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the Aimportant and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

The breadth of the claims and the quantity of experimentation required. The claims are drawn to pharmaceutical compositions and methods of treating tumors in a subject comprising administration of an antisense, optionally expressed from an adenoviral vector under the control of a heat shock promoter, that specifically hybridizes with and inhibits the expression of Ku70. The ability to specifically hybridize with and inhibit the expression of Ku70 in appropriate target cells in vivo and provide treatment

effects are highly unpredictable endeavors. It would therefore require undue experimentation to practice the invention over the broad scope claimed.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting Ku70 expression in target cells in vivo comprising the administration of antisense, and further whereby treatment effects are provided for any tumor in a subject. The specification teaches an increase in radiation and chemotherapeutic sensitivity in Ku70 cells obtained from Ku70 knockout mice. One skilled in the art would not accept on its face the examples given in the specification of gene ablation experiments and further characterization of cells derived from such knockouts as being correlative or representative of the ability to inhibit the expression of Ku70 in appropriate target cells in vivo using antisense and further whereby treatment effects are provided. This is in view of the lack of guidance in the specification and known unpredictability associated with the ability to inhibit the expression of a target gene in vivo and provide treatment effects in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with the inhibition of expression of human Ku70 in an organism, and further whereby treatment effects are provided.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reeves et al and Milner et al, the combination in view of Taniguchi et al and Au-Young et al insofar as the claims are drawn to compositions and methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide, optionally in an adenoviral expression vector comprising a heat shock promoter, that specifically hybridizes with a nucleic acid encoding a DNA dependent protein kinase subunit (Ku70), which antisense inhibits the expression of the target Ku70 subunit.

Reeves et al (J. Biol. Chem., Vol. 264(9): 5047-5052, 1989) teach the polynucleotide sequence encoding DNA-PK subunit Ku70, and the binding of Ku70 to the ends of double stranded DNA in a complex with Ku80 (see especially figure 4 on p. 5050 and the text on p. 5047).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

The primary references of Reeves et al and Milner et al do not teach methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide specifically targeting a nucleic acid

encoding Ku70, and which antisense is in an adenoviral expression vector, operably linked to a heat shock promoter.

Takiguchi et al (Genomics 35: 129-135, 1996) teach the role of mouse and human DNA-PK (comprising the subunits Ku70, Ku80 and DNA-PK catalytic subunit) in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the crucial role of Ku70 in DNA double stranded repair, and the importance in studying the subunits of DNA-PK in human diseases and in immunogenesis (see text on p. 129; p. 133-134).

Au-Young et al (USPN 5,773,580) teach pharmaceutical compositions comprising antisense oligonucleotides for inhibiting a known target gene, as well as teaching adenoviral expression vectors comprising antisense oligonucleotides and ribozymes, which oligonucleotides are operably linked to regulatory elements including an inducible (heat shock) promoter (see esp. col. 10-11, 20-21).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of Ku70 in vitro because its nucleotide sequence had been taught previously by Reeves et al, and Milner et al teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540). Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have expected that

the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides human DNA dependent protein kinase subunits, including Ku70.

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of nucleic acid constructs including antisense and ribozymes in an appropriate target cell, as taught previously by Au-Young et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector, including an adenoviral vector, in order to control the conditions of expression of the operably linked antisense, and in order to control conditions for antisense expression and subsequent inhibition of the antisense's target gene in an appropriate target cell.

One of ordinary skill in the art would have been motivated to target and inhibit the expression of the various subunits of DNA-PK, including Ku70, in order to increase a target cell's sensitivity to DNA damaging agents because Taniguchi et al teach the relationship between increasing cell radiosensitivity or loss of DNA repair function, and loss of functional DNA-PK. One of ordinary skill in the art would have been motivated to inhibit the expression of Ku70 in order to increase a target cell's sensitivity to DNA repair because it was well known in the art that Ku 70 is involved in double stranded

DNA repair and it was also well known that strand repair occurs in cells following DNA damage (e.g. strand breaks). One of ordinary skill in the art would have expected that a cancer cell would undergo DNA repair after its exposure to DNA damaging agents. And one of ordinary skill in the art would be motivated to undermine a cancer cell's ability to repair DNA after treating it with DNA damaging agents in order to eventually undermine that cancer's ability to survive.

One of ordinary skill in the art would have expected that by utilizing appropriate conditions for expression (e.g. induction by heat), the antisense targeting DNA-PK would be expressed upon induction of the heat shock promoter because such induction systems as heat shock promoters have been routinely used as described by Au-Young et al. One of ordinary skill in the art would have been motivated to induce expression of antisense and ribozymes under desired conditions (e.g. upon exposure heat) because induction is a way of controlling the conditions for increased expression of the operably linked antisense and ribozymes, and also a way of controlling the subsequent inhibition of target gene expression following expression of these antisense. In this way, increasing a cell's sensitivity to DNA damaging agents is in turn induced following heat treatment and expression of antisense. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27, 39 and 40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15, 16 and 18-22 of copending Application No. 09/750,410. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 27, 39 and 40 are drawn to compositions and methods for increasing a cell's susceptibility to DNA damaging agents comprising administration of antisense that target and inhibit expression of Ku70 and claims 1, 15, 16, 18-22 of Application No. 09/750,410 are drawn to compositions and methods for increasing a cell's susceptibility to DNA damaging agents comprising administration of liposomal compositions and methods comprising administration of antisense that target and inhibit the expression of Ku70.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices

published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-11-06

TC 1600

JANE ZARA, PH.D.
PRIMARY EXAMINER